CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

NICOSULFURON

Chemical Code # 3829, Tolerance # 51925

4/15/94

I. DATA GAP STATUS

Combined, rat:	**No data gap; no adverse effect**
Chronic toxicity, dog:	**No data gap; no adverse effect**
Oncogenicity, mouse:	**No data gap; no adverse effect**
Reproduction, rat:	**No data gap; no adverse effect**
Teratology, rat:	**No data gap; no adverse effect**
Teratology, rabbit:	**No data gap; possible adverse effect (not developmental1)**
Gene mutation:	**No data gap; no adverse effect**
Chromosome effects:	**No data gap; no adverse effect**
DNA damage:	**No data gap; no adverse effect**
Neurotoxicity:	**Not required for this compound at this time**

Toxicology one-liners are attached.

All record numbers through 115473 were examined.
**** indicates an acceptable study.**
Bold face indicates a possible adverse effect.
File name: T940415

1Increased incidence of abortions

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 043; 115434; "Combined Chronic Toxicity/Oncogenicity Study in IN V9360-27 Two-Year Feeding Study in Rats" (author: Cook, J.C., Haskell Lab. for Toxicology & Industrial Medicine, Newark, DE, Report # 637-89, 12/27/89); IN V9360-27 (90.6% purity) or IN V9360-29 (92.75% purity) administered in diet to 62 rats/sex/dose at 0, 50, 1500, 7500 and 20000 ppm for 2 years; no adverse effects; no compound-related clinical observations or changes in body weight, food consumption, organ weights, hematological, clinical chemistry and urinalysis parameters were detected; necropsy and histopathology did not reveal any abnormal findings; IN V-9360 did not demonstrate any chronic toxicity or oncogenicity when tested at the highest dose level for two years; NOEL (M/F) = 20000 ppm (786 and 1098 mg/kg/day for male and female rats, respectively; no effect at HDT); acceptable; (Leung, 3/25/94).**

CHRONIC TOXICITY, DOG

**** 041; 115431; "Chronic Toxicity Study with IN V9360-27: One-Year Feeding Study in Dogs" (author: Cook, J.C., Haskell Lab. for Toxicology & Industrial Medicine, Newark, DE, Report # 390-89, 11/2/89); IN V9360-27 (90.6% purity) administered in diet to 5 beagle dogs/sex/dose at 0, 250, 5000, or 20000 ppm for 1 year; all animals survived the study until scheduled termination; no compound-related clinical observations or changes in body weight and food consumption were detected; high dose males exhibited increased mean relative liver weight (122% of control, $p < 0.05$) without any abnormal histopathological alterations and was not considered to be an adverse effect; there were no other gross or microscopic findings due to dietary exposure to IN V9360-27; NOEL (M) = 5000 ppm or 141.1 mg/kg/day (based on marginal changes in relative liver weight), (F) = 20000 ppm or 563.5 mg/kg/day (no effect at HDT); acceptable; (Leung, 3/23/94)**

ONCOGENICITY, MOUSE

**** 044; 115436; "Oncogenicity Study with IN V9360-27 Eighteen-Month Feeding Study in Mice" (Cook, J.C., Haskell Lab. for Toxicology & Industrial Medicine, Newark, DE, Report # 645-89, 12/7/89); IN V9360-27 (90.6% purity) administered in the diet to 80 mice/sex/dose at 0, 25, 250, 2500, and 7500 ppm for 18 months; no treatment-related clinical observations or effects on body and organ weights, food consumption, hematology, clinical chemistry, gross necropsy and histopathology were detected; no adverse effects; IN V9360-27 did not demonstrate any chronic toxicity or carcinogenic potential; NOEL (M/F) = 7500 ppm (953.3 and 1259.5 mg/kg/day for male and female mice, respectively; no effect at HDT); acceptable; (Leung, 3/28/94)**

REPRODUCTION, RAT

**** 051, 052; 115466, 115468; "Reproductive and Fertility Effects with IN V9360-27 Multigeneration Reproduction Study in Rats" (author: Mullin, L.S., Haskell Lab. for Toxicology & Industrial Medicine, Newark, DE, Report # 429-89, 12/13/89); IN V9360-27 (90.6% purity) administered in the diet to 30 rats/sex/generation at 0, 250, 5000, and 20000 ppm for 2 generations; test article administration had no effect on clinical observations, mortality, gross pathology or reproductive parameters; microscopic examination revealed a low incidence of bilateral testicular degeneration in 0, 250, 5000, and 20000 ppm $F_{\leftarrow}$ males (0/30, 1/30, 3/30, and 4/30, respectively); absolute and relative testicular weights, mating and fertility indices of male rats in the $F_{\leftarrow}$ and $F_{\leftarrow}$ generations were not affected; therefore, the slightly higher incidence of testicular degeneration was not considered to be toxicologically significant; no adverse effects; parental NOEL (M/F) = reproductive NOEL = 20000 ppm (1154.9 and 1508.2 mg/kg/day for male and female rats, respectively, no effect at HDT); acceptable; (Leung, 3/30/94).**

TERATOLOGY, RAT

**** 057; 115473; Teratogenicity Study of IN V9360-27 in Rats, Alvarez, L.; 833; Rat; E.I. du Pont de Nemours and Company; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; HLR 611-88; 12/9/88; IN V9360-27, purity: 90.6%; 25 females/group; Doses: 0 (I), 200 (II), 1000 (III), 2500 (IV), 6000 (V) mg/kg, by gavage, day 7 through day 16 of gestation; No mortality; Clinical signs: (maternal) no treatment effect upon body weight or food consumption, no treatment-related signs or post-mortem findings, no treatment-related reproductive effect; (fetal) no treatment-related effect on weight or incidence of malformations, increased number of total variations (V) (no notable increase of a particular variation); no adverse effect; Maternal NOEL: 6000 mg/kg, Developmental NOEL: 2500 mg/kg (based on increased occurance of developmental variations (total) in the fetuses of the 6000 mg/kg group); Study acceptable. (Moore, 3/29/94)**

TERATOLOGY, RABBIT

**** 056; 115472; Teratogenicity Study in IN V9360-27 in Rabbits, Hurtt, M.E.; 833; Rabbit; Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; HLR 694-88; 12/8/88; IN V9360-27, purity: 90.6%; 20 females/group; Doses: 0 (I), 100 (II), 500 (III), 1000 (IV), 2000 (V) mg/kg/day, by gavage, day 7 through day 19 of gestation; Mortality: (II) 1 (dosing accident), (III) 1 (died on day 23 after aborting), (V) 3, 1 (dosing accident), 1 (spontaneous death on day 19), 1 (died on day 26 after aborting); Clinical signs: (maternal) reduced body weight gain in higher dosing groups, reduced food consumption, diarrhea and vaginal discharge (V), increased incidence of abortions (III, IV, V), increased number of early resorptions (III); (fetal) decreased body weight (IV), no treatment related malformations or variations; no adverse effect indicated; possible maternal adverse effect: increased incidence of abortions; Maternal NOEL: 100 mg/kg/day (based on incidence of abortions in 500 mg/kg/day treatment group), Developmental NOEL: 500 mg/kg/day**

(based on significantly decreased fetal body weight in 1000 mg/kg/day treatment group); Study acceptable. (Moore, 3/22/94)

GENE MUTATION

**** 51925-046; 115445; mutagenicity; 842; Haskell Laboratory for Toxicology & Industrial Medicine, du Pont & Co., Newark, DE; "Mutagenicity Evaluation of IN V9360-27 in the CHO/HGPRT Assay"; author, K.S. Bentley; 7/14/88; report #429-88; IN V9360-27 (Nicosulfuron; 90.6% purity); doses (%S9): 0, 4, 20, 40, 200, & 465 mg/ml (max. concentration based on solubility of stock solution); 5x105 cells/25cm2 flask plated on day 0, test article-containing medium added on day 1; -S9, exposure time was 18-19 hr; +S9, exposure time was 5 hr; cytotoxicity determined by replating 200 cells/60 mm dish (6 dishes) and counting resultant colonies 6-8 days later; mutagenicity was determined by replating 106 cells/100 mm dish, subculturing 2x over the next 7 days, & replating at 2x105/100 mm dish in the presence of 6-thioguanine (6-TG); after 6-8 days the resultant 6-TG resistant colonies were counted; no cytotoxicity was evident through 465 mg/ml; no increase in 6-TG resistance was detected under any condition (despite success of positive controls), thus IN V9360-27 is not considered mutagenic in this system; Acceptable. (Rubin, 3/15/94)**

51925-049; 115457; mutagenicity; 842; Haskell Laboratory for Toxicology & Industrial Medicine, du Pont & Co., Newark, DE; "Mutagenicity Testing of INV-9360-7 in the Salmonella typhimurium Plate Incorporation Assay"; author, V.L. Reynolds; 11/23/88; report #734-88; INV-9360-7 (Nicosulfuron; 90.4% purity); strains/doses (%S9): TA1535/0, .1, .25, .5, .75, 1 mg/plate; TA97a/0, .02, .04, .06, .08, .1 mg/plate; TA98/0, .1, .25, .5, .75, 1 mg/plate; TA100/0, .1, .5, 1, 5, 10 mg/plate; 2 independent trials; dosing based on cytotoxicity studies conducted in minimal histidine medium; no evidence for mutagenicity (i.e. an increase in revertants arising in low-histidine agar) in any tester strain, regardless of the presence or absence of S9 microsomes and despite the success of the positive control compounds; Unacceptable (but possibly upgradeable with submission of 1. clarifications of cytotoxicity technique and 2. cytotoxicity data used to justify dose ranges for all tester strains). (Rubin, 3/14/94)

CHROMOSOME EFFECTS

51925-045; 115444; structural chromosome abnormalities; 843; Haskell Laboratory for Toxicology & Industrial Medicine, du Pont & Co., Newark, DE; "In Vitro Evaluation of IN V9360-27 for Chromosome Aberrations in Human Lymphocytes"; author, D.A. Vlachos; 7/26/88; report #470-88; IN V9360-27 (Nicosulfuron, 90.6% purity); lymphocytes cultured from 1 male and 1 female donor (cytotoxicity determination utilizes only the male donor); division stimulated w/1.5% PHA; duplicate cultures were exposed to test article at each dose (%S9); 3-hr exposure followed by BrdU staining (for generation time assessment in cytotoxicity test only) and colcemid treatment to arrest cells in metaphase; cells were centrifuged, fixed, & further stained; 50 cells from each replicate were examined for chromosomal aberrations (only cells w/46 centromeres were scored);

doses for cytotoxicity test: 0, 300, 400, & 470 mg/ml; no evidence for change in average generation time (interpreted as no cytotoxicity); doses for aberration test: 0, 40, 200, 400, 470 mg/ml; no evidence for increase in any type of aberration under any condition despite success of positive controls (-S9, 0.35 mg/ml mitomycin C; +S9, 10 mg/ml cyclophosphamide); Unacceptable (but possibly upgradeable with submission of rationale for the choice of exposure time). (Rubin, 3/16/94)

**** 51925-048; 115455; structural chromosome abnormalities; 843; Haskell Laboratory for Toxicology & Industrial Medicine, du Pont & Co., Newark, DE; "Mouse Bone Marrow Micronucleus Assay of IN V9360-27"; author, D.A. Vlachos; 7/18/88; report #428-88; IN V9360-27 (Nicosulfuron, 90.6% purity); 500, 2500, & 5000 mg/kg body wt. were administered by gavage in corn oil (15 ml/kg); animals dosed at 500 & 2500 mg/kg were sacrificed at 24 hr post dose (5/sex); those at 0 (vehicle controls) & 5000 mg/kg were sacrificed at 24, 48 & 72 hr (6/sex/sacrifice at the high dose; the extra animal allowed for possible mortality); positive controls: 5/sex treated w/40 mg cyclophosphamide (CP)/kg b.w. and sacrificed at 24 hr; no test article-induced statistically significant increase over negative controls was observed in the number of micronucleated polychromatic cells at any time or dose despite the success of the positive controls; no significant depression of the ratio of polychromatic to normochromatic cells; thus test article did not induce micronuclei in bone marrow cells or bone marrow toxicity under the conditions of this assay; Acceptable. (Rubin, 3/17/94)**

DNA DAMAGE

**** 51925-047; 115451; other genetic effects; 844; Haskell Laboratory for Toxicology & Industrial Medicine, du Pont & Co., Newark, DE; "Assessment of IN V9360-27 in the In Vitro Unscheduled DNA Synthesis [UDS] Assay in Rat Primary Hepatocytes"; author, K.S. Bentley; 5/23/88; report #302-88; IN V9360-27 (Nicosulfuron, 90.6% purity); primary hepatocytes were pooled from 2 livers for each trial; chamber slides containing hepatocyte plating medium were inoculated w/5x105 cells/chamber after which they were allowed to attach; 4 cultures/dose; treatment medium included test article and 3H-thymidine (3H-TdR); 18-hr exposure; doses: 0, .04, .4, 1.2, 4.1, 12, 41, 122, 409, & 470 mg/ml (high dose determined by solubility limit in the stock solution); cytotoxicity evaluation: LDH activity in medium after exposure; UDS evaluation: autoradiography to detect 3H-TdR incorporation after exposure (25 cells/culture evaluated); neither cytotoxicity nor UDS was evident at any concentration tested despite success of the positive control (.022 and .22 mg/ml 2-acetyl aminofluorene) in the UDS assay; Acceptable. (Rubin, 3/15/94)**

NEUROTOXICITY

Not required for this compound at this time.